Global Veterinaria 22 (3): 121-127, 2020
ISSN 1992-6197

DOI: 10.5829/idosi.gv.2020.121.127

Veterinary Vaccines Handling, Transportation and Storage: Factors Challenging their Efficacy and Their Adverse Effects to the Host

Samrawit Yohannes, Bashahun G. Michael and Waktole Yadeta

School of Veterinary Medicine, College of Agriculture and Veterinary Medicine,
Jimma University, P.O. Box: 307, Jimma, Ethiopia

Abstract: This review investigated the major types of veterinary vaccines developed, the protocol of Handling, transporting and storing of them, factors challenging their efficacy and adverse effects of them to the host. Veterinary vaccines are a key component of livestock disease prevention and control worldwide. They have a major role in protecting animal health, reducing animal suffering, enabling efficient production of food animals and greatly reducing the need for antibiotics to treat food and companion animals. Common veterinary vaccines available are modified-live virus vaccines, killed vaccines (inactivated vaccines), toxoid vaccines, polynucleotide vaccines, subunit vaccines, virus-vectored vaccines, gene-deleted vaccines, recombinant viral proteins and valence vaccines. Quality of these vaccines are essential for the maintenance of animal health. To ensure these qualities, Vaccines are supplied with specific instructions such as dose rate, storage and administration procedures, any side effects that may potentially occur, withdrawal periods and the expiry date of the product. These instructions are important and must be understood and followed to ensure that the product does what it is supposed to do. However, these important activities can be challenged by vaccine factors, host factors, environmental factors and the human factors resulting in poor vaccine storage, handling, transportation and administration. Therefore, Care should be taken on vaccine handling, storing, transporting and administrating to ensure vaccine potency and maximizing effectiveness.

Key words: Veterinary Vaccines · Types · Handling · Storage · Transportation

INTRODUCTION

Livestock are vital to the livelihoods of the world's rural population. The sector has been contributing considerable portion to the economy of the developing countries and still promising to rally round the economic development [1].

A vaccine is any preparation intended to produce immunity to a disease by stimulating the production of antibodies [2]. Veterinary vaccines are a key component of livestock disease prevention and control worldwide.

They have a major role in protecting animal health, reducing animal suffering, enabling efficient production of food animals and greatly reducing the need for antibiotics to treat food and companion animals [3].

There are different types of vaccines; Modified-live virus vaccines, Killed vaccines (Inactivated vaccines), Toxoid vaccines, Polynucleotide vaccines, Subunit vaccines, Virus-vectored vaccines, Gene-deleted vaccines, Recombinant viral proteins, Valence vaccines and others. But all vaccines have one thing in common. They are delicate biological substances that can become less effective or be destroyed if they are: frozen; allowed to get too hot; and/or exposed to direct sunlight or fluorescent light. If vaccines are exposed to such conditions, they may lose their potency, i.e. the capacity to induce an immune response in the vaccinated animal [4].

Quality of veterinary vaccines are essential for the maintenance of animal health [5]. To ensure these qualities, Vaccines are supplied with specific instructions such as dose rate, storage and administration procedures, any side effects that may potentially occur, withdrawal periods and the expiry date of the product. These instructions are important and must be understood and followed to ensure that the product does what it is

Corresponding Author: Waktole Yadeta, School of Veterinary Medicine, College of Agriculture and Veterinary Medicine, Jimma University, P.O. Box: 307, Jimma, Ethiopia.

supposed to do [2]. However, these important activities can be seriously compromised by poor vaccine storage, handling and transportation [6].

For vaccine storage the important criteria are: establishing Storage and Handling Policies, Using Proper Storage Equipment, Ensuring optimal operation of storage units, Maintaining Correct temperatures, maintaining daily temperature logs, taking emergency action as needed when vaccines are exposed to improper storage conditions [7]. Proper supplies are essential for the safe transport of vaccines and proper packing should be maintained before transporting [8]. During transportation, refrigerated and frozen vaccines must maintain their optimal temperature values to preserve their potency. Means of transport used must maintain the potency of the vaccine as it is [9].

Awareness of vaccine transport, storage and handling issues is greater in human medicine than in veterinary medicine, due to the risk of epidemic diseases such as polio, influenza and smallpox [7]. By reviewing research on human vaccine protocol, veterinary professionals can learn a great deal about proper vaccine handling and storage [10]. In many developing countries, there are problems related to vaccine efficacy and continuous outbreaks in vaccinated animals [11]. This might be due to improper production or storage, transportation and handling of the vaccines. Therefore, the objectives of this review are to review:

- ✓ Major types of veterinary vaccines developed
- ✓ The protocol of handling, transporting and storing of veterinary vaccines
- ✓ Factors Challenging Vaccine Efficacy and
- ✓ Adverse Effects of Vaccines to the Host.

Types of Veterinary Vaccines

Modified-live Virus Vaccines: Modified-live virus vaccines (MLV) contain whole viruses that have been altered such that, their ability to cause disease has been taken away. Vaccine manufacturers typically achieve this by making the microbe grow under prolonged or slightly abnormal growing conditions [12]. MLV vaccines are typically packaged in two vials one containing a freeze-dried cake that contains the modified microbes and the other containing the diluents, which re-suspends the microbes [13]. They offer better stimulation of the immune response and require lower doses of the bacteria or viruses. Ideally they should not cause any clinical signs of disease [14]. MLV vaccine provides rapid onset of immunity and a single dose of can offer protection in healthy animals [15]. It has better ability to overcome maternal antibody interference [16].

Killed Vaccines (Inactivated Vaccines): Killed vaccines comprise whole viruses or bacteria which have been deactivated by heat or chemical treatment. They are typically coupled with an adjuvant that acts as a stimulant to increase the animal's immune response [12]. Adjuvants are compounds that non-specifically stimulate the immune system to respond to and sluggish down the body's removal of the injected inactivated microbes [13]. Preparation of killed vaccines may take the route of heat or chemicals. The chemicals used include formaldehyde or beta- propiolactone. The traditional agent for inactivation of the virus is formalin. Excessive treatment can destroy immunogenicity whereas insufficient treatment can leave infectious virus capable of causing disease. A good example for inadequately inactivated vaccine is, soon after the introduction of inactivated polio vaccine, there was an outbreak of paralytic poliomyelitis in the USA [15]. That incident led to a review of the formalin inactivation procedure and other inactivating agents available now, such as beta-propiolactone. The major disadvantage of killed vaccines is that it takes much longer to provide protection [13].

Toxoid Vaccines: Toxoids are used as vaccines because they induce an immune response to the original toxin or increase the response to another antigen since the toxoid markers and toxin markers are preserved [17]. For bacteria that secrete toxins, or harmful chemicals, a toxoid vaccine might be the answer. These vaccines are used when a bacterial toxin is the main cause of illness. Scientists have found that they can inactivate toxins by treating them with formalin, a solution of formaldehyde and sterilized water. Such "detoxified" toxins, called toxoids are safe for use in vaccines [18]. The immune system produces antibodies that lock onto and block the toxin. Once the toxin is inactivated, it's called a toxoid and it can no longer cause harm. A vaccine against tetanus is an example of toxoid vaccine [19]. Not all toxoids are for micro-organisms; for example, Crotalusatrox toxoid is used to vaccinate dogs against rattlesnake bites. Toxoid vaccines are safe for there is no possibility of reversion to virulence [20].

Polynucleotide Vaccines: Animals may also be immunized by injection of DNA encoding viral antigens [10]. This DNA can be inserted into a bacterial plasmid, a piece

of circular DNA that acts as a vector. When the genetically engineered plasmid is injected, it can be taken up by host cells. The DNA is then transcribed and mRNAs are translated to produce vaccine protein. Transfected host cells thus express the vaccine protein in association with major histo-compatibility complex class I molecules. This can lead to the development of not only neutralizing antibodies but also cytotoxic T cells [2]. This approach has been applied experimentally to produce vaccines against the viruses that cause avian influenza, lymphocytic choriomeningitis, canine and feline rabies, canine parvo, bovine viral diarrhea, feline immunodeficiency virus related disorders, feline leukemia, pseudo rabies, foot-and-mouth disease, bovine herpesvirus-1 related disease and Newcastle disease. As they can produce a response similar to that induced by attenuated live vaccines, these polynucleotide vaccines are ideally suited for use against organisms that are difficult or dangerous to grow in the laboratory [10].

Subunit Vaccines: Subunit vaccines, like inactivated whole-cell vaccines, do not contain live components of the pathogen. They contain only viral or bacterial antigens which can trigger an immune response [20]. A recent example is a new synthetic vaccine against foot and mouth disease [14]. Subunit vaccines contain only parts of the bacteria or virus of interest. Like inactivated vaccines, they do not contain live components and are considered as very safe [2].

Virus-Vectored Vaccines: Another method to produce a highly effective living vaccine is to insert the genes that code for protection antigens into an avirulent vector organism. These vaccines are created by deleting genes from the vector and replacing them with genes coding for antigens from the pathogen. The recombinant vector is then administered as the vaccine and the inserted genes express the antigens when body cells are infected by the vector virus. The vector may be attenuated so that it will not be shed from the vaccinated, or it may be host-restricted so that it will not replicate itself within the tissues of the vaccinate [21]. Virus-vectored vaccines are well suited for use against organisms that are difficult or dangerous to grow in the laboratory [10].

Gene-Deleted Vaccines: Attenuation of viruses by prolonged tissue culture can be considered a primitive form of genetic engineering. [10] Ideally, this resulted in the development of a strain of virus that was unable to cause disease. This was often difficult to achieve and reversion to virulence was a constant hazard. Molecular genetics techniques now make it possible to modify the genes of an organism so that it becomes irreversibly attenuated. Deliberate deletion of the genes that code for proteins associated with virulence is an increasingly attractive procedure [12]. For example, gene-deleted vaccines were first used against the pseudorabies herpes virus in swine. In this case, the thymidine kinase gene was removed from the virus. Herpes virus requires thymidine kinase to return from latency. Viruses from which this gene has been removed can infect neurons but cannot replicate and cause disease [21].

Recombinant Viral Proteins: Recombinant vector vaccines are experimental vaccines similar to DNA vaccines, but they use an attenuated virus or bacterium to introduce microbial DNA to cells of the body [18]. An alternative application of recombinant DNA technology is the production of hybrid virus vaccines. The best known example is vaccinia; the DNA sequence coding for the foreign gene is inserted into the plasmid vector along with a vaccinia virus promoter and vaccinia thymidine kinase sequences. The resultant recombination vector is then introduced into cells infected with vaccinia virus to generate a virus that expresses the foreign gene. The recombinant virus vaccine can then multiply in infected cells and produce the antigens of a wide range of viruses. The genes of several viruses can be inserted, so the potential exists for producing polyvalent live vaccines [22].

Purified or recombinant products often require the same booster schedule and time to onset as a killed vaccine; they are also generally costlier than traditional MLV or killed vaccines. The recombinant vaccine for canine distemper has been shown to provide rapid protection similar to the MLV vaccines and works well in young puppies as well [15].

Valence Vaccines: Vaccines may be monovalent or multivalent (polyvalent). A monovalent vaccine is designed to immunize against a single antigen or single microorganism. A multivalent or polyvalent vaccine is designed to immunize against two or more strains of the same microorganism, or against two or more microorganisms. In certain cases, a monovalent vaccine may be preferable for rapidly developing a strong immune response [19].

Vaccine Handling, Storage and Transportation

Handling: For lyophilized vaccines, only the diluents that are provided with the vaccine should be used. Generally the diluents do not need to be refrigerated, but it is usually more convenient to keep them in refrigerator with the corresponding vaccine [13]. A new sterile syringe and needles should always be used for drawing up and administer vaccine. A vaccine should not be reconstituted or draw up into the syringe until needed. Not only may the reconstituted vaccine be more temperature sensitive than the non-reconstituted vaccine, but there is also a risk of bacterial contamination and overgrowth if the syringe is left for a prolonged period. In addition, there is risk of "mistake identity" because many vaccines look similar in the syringe [23].

Storage: Virtually all vaccines used in small and large animal veterinary medicine, includes lyophilized (freeze- dried) and liquid forms, must be stored in the dark between 35°F (2°C) and 45°F (7°C). Few veterinary vaccines (e.g., some poultry and fish vaccines) must be kept frozen and technicians working with frozen vaccines should contact the manufactured for specific storage instructions [24]. Vaccine requiring refrigeration must be stored in a designed refrigerator. This should be a standard-size refrigerator with a separate freezer compartment-not a mini dormitory-style refrigerator-to ensure better temperature control. The temperature inside a refrigerator can vary, with Warmer temperatures in the door and vegetable bins and colder temperature near the cold air outlet from the freezer to the refrigerator [25]. For this reason, vaccine should be kept in the center of refrigerator, far enough from the freezer compartment to prevent them from freezing, storing jugs of water in the refrigerator may also help prevent temperature fluctuations [26].

Vaccine should be kept in their original packaging and boxes should be rotated so that the newest batch (with the latest expiration date) is in the back and is used last. Food and beverages should not be stored in the vaccine refrigerator; doing so violates occupational safety and health administration regulations. In addition, frequently opening the refrigerator to retrieve food can also lead to temperature fluctuations [24].

In case of power outage, the refrigerator should not be opened until power has been restored; when power is restored the temperature inside the refrigerator should be immediately checked and logged, along with the duration of power outage. Affected vaccine should not be discarded but should be marked and kept separated from the unaffected vials. The manufacturers of the vaccines should be called for guidance. Depending on the duration outage and the ending temperature in the refrigerator, the vaccine may still be usable. If a prolonged power outage is anticipated (e.g. because of hurricane or other natural disaster), the vaccines may be moved off-site to allocation that will not be affected [27].

Transportation: Vaccines are frequently transported in large animal practice and in small animal house call practice. [6] The cold chain must be maintained during transport. Vaccines should be kept in insulated cooler. Frozen ice packs or refrigerated packs should be used as needed to maintain temperature between 35°F (2°C) and 45°F (7°C). The temperature in the cooler should be monitored and logged immediately before and after transport [28]. A layer of insulation should be tucked between the vaccine box and the ice packs to prevent direct contact, which could result in freezing temperature in the vaccine vial. The cooler should be kept in the passenger cabin of the vehicle. Temperatures in the trunk or truck bed could get too hot in summer or too cold in winter [26].

Factors Challenging Vaccine Efficacy

Vaccine Factors: Veterinary vaccines whether attenuated or non-infectious from the different manufacturers can vary in their potency, efficacy and duration of immunity [29]. Attenuated vaccines tend to induce stronger and long-lasting immunity than non-infectious vaccine. Non-infectious vaccines include killed, toxoid; subunit and DNA vaccines are safer and more stable than attenuated vaccines [30]. However, due to risk of using live vaccines in pregnant or immunosuppressed animals as well as the risks of shedding vaccine virus, non-infectious is preferred for some diseases [31].

Vaccine, if used properly, induced protection from challenge in a high percentage of vaccinated animals. This is achieved by presenting the correct antigen in a safe manner to the host's immune system. However, wild type organisms change with time and place. Vaccines that were effective may become ineffective due to antigenic drift [32].

Host Factors: Host-related factors can affect vaccine efficacy, of which host genetics, immune status, age, breed, health or nutritional status can be associated with vaccine failures [29]. For instance, animals who are

malnourished, like those who are ill, may not respond adequately to a vaccination. Poor nutrition, such as Vitamin A, Vitamin E and selenium deficiencies and restricted protein or calories can result in suppression of the immune system [33].

Environmental Factors: The atmospheric conditions (temperature, lighting, ventilation, etc.) can influence efficacy of vaccine if it has been utilized carelessly [29]. While vaccination program may be adequate to control infectious disease under normal condition of exposure, it should be remembered that they may not protect under severe condition of challenge. This situation has been observed in kittens infected with feline parvovirus (FPV). In many cases, FPV was not suspected initially as a cause of death because vaccination was performed in the households in which diseases occurred. Disease was thought to develop as a result of accumulation of virus in an environment that either overcame vaccinal immunity in the affected kittens or infected the kittens in the period between the weaning of maternal antibodies and the administration of the vaccination [6].

The Human Factor

Inappropriate Administration: Vaccines are developed to be given by a certain route; intranasal route, subcutaneously, or intramuscularly. If a vaccine is administered by a route different from the route for which it was developed, it may not be effective and could cause considerable harm [34].

Equipment: The equipment used must be checked and prepared the day before so that the vaccination operation can be started as early as possible. It can be useful to draw up procedures that list the necessary administration material (including spares) and that describe how the preparation (cleaning, greasing) and the checks should be carried out (calibrating the syringes, operating the nebulizer). It is important not to overlook the water used in sprayed administrations, the solvents (for the wing-web and eye drop method) as well as water treatments (for administration via drinking water). It is also preferable to prepare in advance the clothing to be worn by each person [35].

Incorrect Storage: Incorrect handling or storage of the vaccine, resulting in an in-effective vaccine being administered that will not provide protection e.g., the toxicity of dimethyl sulfoxide (DMSO) for Babesia parasites at temperature above freezing is a serious constraint on the infectivity of the vaccine. After thawing the vaccine at between 37 and 40°C, it must be injected immediately. It has been shown that if the vaccine is thawed slowly in melting ice and kept in melting ice, it is still infective for up to 8 hours without showing significant changes in the prepatent period. However, to ensure on margin of safety, it is recommended that the vaccine be used within 4 hours of thawing [29]. To achieve the best possible results from vaccines, vaccine providers should carefully follow the recommendations found in each vaccine's package insert for storage, handling and administration. Other steps to help ensure vaccine safety include: inspecting vaccines upon delivery and monitoring refrigerator and freezer temperatures to ensure maintenance of the cold chain; rotating vaccine stock so the oldest vaccines are used first; never administering a vaccine later than the expiration date; administering vaccines within the prescribed time periods following reconstitution; waiting to draw vaccines into syringes till immediately prior to administration and never mixing vaccines in the same syringe unless they are specifically approved for mixing [7].

Techniques: Provision of written standard operating procedures and training in their use is essential. It is common to detect serious malpractices when monitoring vaccination practice in the field, which result from inadequate training of vaccination staff [34]. These include the use of un-cooled boiled water for reconstituting CBPP vaccines; the use of water rather than saline to reconstitute vaccine; the use of hot syringes to draw up vaccine; the use of incorrectly calibrated syringes; retaining reconstituted vaccine for much longer than its effective retention time; transporting vaccine at ambient temperatures or even in sun-heated cars from office refrigerator to field; and lack of cold chain during importation and from central storage to field units [6].

Adverse Effects of Vaccines to the Host: Common risks associated with vaccines are residual virulence and toxicity, which may cause injection-site reactions, depression, allergic responses, disease in immune-deficient hosts, neurologic complications and rarely, contamination with other live agents.

Vaccines that contain killed gram-negative organisms may also contain bacterial cell-wall components that stimulate release of interleukin-1 and can cause fever and leukopenia and occasionally abortion [21].

In addition to potential toxicity, vaccines, like any antigen, may provoke hypersensitivity. For example, rapid allergic reactions (type I hypersensitivity) may occur in response to any of the antigens found in vaccines, including those from eggs or tissue-culture cells [36]. All forms of hypersensitivity are more commonly associated with multiple injections of antigen; therefore, they tend to be associated with use of inactivated products. Immune complex (type III) reactions are also potential hazards of vaccination. These may cause an intense local inflammatory reaction or a generalized vascular disturbance such as purpura. An example of a type III reaction is clouding of the cornea in dogs vaccinated against canine adenovirus 1 [37]. Delayed (type IV) hypersensitivity reactions, expressed as granuloma formation and may develop at the site of inoculation in response to the use of depot adjuvants. Some chronic inflammatory reactions to long-acting feline vaccines may eventually lead to development of a fibro sarcoma at the injection site in cats [21].

CONCLUSIONS AND RECOMMENDATIONS

Veterinary vaccines are a key component of livestock disease prevention and control worldwide. Modified-live virus vaccines, killed vaccines (inactivated vaccines), toxoid vaccines, polynucleotide vaccines, subunit vaccines, virus-vectored vaccines, gene-deleted vaccines, recombinant viral proteins and valence vaccines are among the types of veterinary vaccines available currently. Quality of these vaccines are essential and to ensure these qualities, they are supplied with specific instructions from manufacturers. However, efficacy of these vaccines can be challenged by vaccine factors, host factors, environmental factors and the human factors resulting in poor vaccine storage, handling, transportation and administration. Therefore, in light with above concluding remarks, the following recommendations are suggested:

- Care should be taken on vaccine handling, storing, transporting and administrating to ensure vaccine potency and maximizing effectiveness.
- There should be training program to people who are involved in vaccination, vaccine storage and handling activities.

Abbreviations:

CBPP Contagious bovine pleuropneumonia
DMSO Dimethyl sulfoxide
DNA Deoxyribonucleic Acid
FPV Feline Parvovirus
MLV Modified live vaccine
mRNA Messenger Ribonucleic Acid

REFERENCES

1. Zeleke, B., 2007. Status and Growth Trend of Draught Animals Population in Ethiopia. J. Dairy Vet. Anim. Res., 6(1): 238-241.
2. Jodar, L., P. Duclos, J.B. Milstien, E. Griffiths and M.T. Aguado, 2001. Ensuring vaccine safety in immunization programmes-a WHO perspective. Vaccine, 19(13-14): 1594-1605.
3. Christine Ahlers, Robyn Alders, Brigitte Bagnol, Ana Bela Cambaza and Mohamed Harun, 2009. Improving village chicken production: A manual for field workers and trainers. Australian Centre for International Agricultural Research (ACIAR).
4. Ford, R.B., (ed), 2001. Vaccines and vaccination: The strategic issues. Vet. Clin. N Am., 31(3): 439-453.
5. Lubroth, J., M.M. Rweyemamu, G. Viljoen, A. Diallo, B. Dungu and W. Amanfu, 2007. Veterinary vaccines and their use in developing countries. Revue Scientifique et Technique-Office International des Epizooties, 26(1): 179.
6. Day, M.J., M.C. Horzinek and R.D. Schultz, 2010. WSAVA guidelines for the vaccination of dogs and cats. Journal of Small Animal Practice, 51(6): e1-e32.
7. Centers for Disease Control and Prevention, 2003. Guidelines for maintaining and managing the vaccine cold chain. MMWR. Morbidity and Mortality Weekly Report, 52(42): 1023.
8. Rogers, B., K. Dennison, N. Adepoju, S. Dowd and K. Uedoi, 2010. Vaccine cold chain: part 1. Proper handling and storage of vaccine. Aaohn Journal, 58(9): 337-346.
9. Chen, D. and D. Kristensen, 2009. Opportunities and challenges of developing thermostable vaccines. Expert Review of Vaccines, 8(5): 547-557.
10. Meeusen, E.N., J. Walker, A. Peters, P.P. Pastoret and G. Jungersen, 2007. Current status of veterinary vaccines. Clin Microbiol Rev., 20(3): 489- 510.
11. Molla, W., K. Frankena, G. Gari and M.C. de Jong, 2017. Field study on the use of vaccination to control the occurrence of lumpy skin disease in Ethiopian cattle. Preventive veterinary medicine, 147: 34-41.

12. Gunn, D., K.S. Jensen, S. Williams, C. Parsons, T. Hudson and J. England, 2013. Cattle Vaccine Handling and Management Guideline, University of Idaho.
13. Daly, R. and A. Price, 2010. Livestock Vaccines: How They Work and How to Ensure They Do Their Job.
14. Postnote, 2013. Livestock Vaccines, the Parliamentary Office of Science and Technology, 7 Millbank, London. Available at. www.parliament.uk/post.
15. Miller, L. and S. Zawistowski, eds., 2012. Shelter medicine for veterinarians and staff. John Wiley & Sons.
16. Ada, G., 2001. Vaccines and vaccination. New England Journal of Medicine, 345(14): 1042-1053.
17. Matsuda, M., 2002. Research Foundation for Microbial Diseases of Osaka University (BIKEN), Tetanus toxin functional fragment antigen and tetanus vaccine. U.S. Patent, 6: 372,225.
18. The National Institute of Allergy and Infectious Diseases (NIAID), 2013. Types of Vaccines, Last syndicated, July 23, 2013.
19. Coastal Carolina Research Center (CCRC), 2013. Clinical research trials and investigational drug studies: Types of Vaccines, 1156 Bowman Rd, Suite 102 Mt. Pleasant, SC 29464.
20. WHO, 2016. Vaccine Safety Basics: Module 2-Toxoid Vaccines. Available at. http://vaccine-safety training.org/copyright.html.
21. Tizard, I.R., 2017. Veterinary Immunology-E-Book. Elsevier Health Sciences.
22. Nascimento, I.P. and L.C.C. Leite, 2012. Recombinant vaccines and the development of new vaccine strategies. Brazilian Journal of Medical and Biological Research, 45(12): 1102-1111.
23. Kroger, A.T., W.L. Atkinson, E.K. Marcuse and L.K. Pickering, 2006. General recommendations on immunization; recommendations of the Advisory Committee on Immunization Practices (ACIP).
24. Pastoret, P.P., 1999. Veterinary vaccinology. Comptes Rendus de l'Académie des Sciences-Series III-Sciences de la Vie, 322(11): 967-972.
25. Hunter, S., 1989. Storage of vaccines in general practice. British Medical Journal, 299(6700): 661.
26. Muegge, S., 2012. Protecting refrigerated vaccines with water bottles: an evidence-based strategy. American Journal of Nursing, 112: 61-69.
27. Chojnacky, M., W. Miller, D. Ripple and G. Strouse, 2009. Thermal analysis of refrigeration systems used for vaccine storage. US Department of Commerce, National Institute of Standards and Technology.
28. Weir, E. and K. Hatch, 2004. Preventing cold chain failure: vaccine storage and handling. Cmaj, 171(9): 1050-1050.
29. Rashid, A., K. Rasheed and M. Akhtar, 2009. Factors influencing vaccine efficacy: a general review. J. Anim Plant Sci., 19: 22-25.
30. Lee, N.H., J.A. Lee, S.Y. Park, C.S. Song, I.S. Choi and J.B. Lee, 2012. A review of vaccine development and research for industry animals in Korea. Clinical and Experimental Vaccine Research, 1(1): 18-34.
31. Potter, A. and V. Gerdts, 2008. Veterinary vaccines: alternatives to antibiotics ?, Animal Health Research Reviews, 9(2): 187-199.
32. Wilson, R., 1994. Influenza vaccination. Thorax, 49(11): 1079.
33. Vlasova, A.N., S. Takanashi, A. Miyazaki, G. Rajashekara and L.J. Saif, 2019. How the gut microbiome regulates host immune responses to viral vaccines. Current opinion in Virology, 37: 16-25.
34. Objio, T., 2019. Vaccine storage and handling and vaccine administration.
35. Chiodini, J., 2014. Safe storage and handling of vaccines. Nursing Standard, 28(25).
36. Bellanti, J.A., 1975. Adverse effects of viral vaccines. In Viral Immunology and Immunopathology (pp: 327-339). Academic Press.
37. Dhein, C.R. and J.R. Gorham, 1986. Host response to vaccination. Veterinary Clinics of North America: Small Animal Practice, 16(6): 1227-1245.